REMARKS

Specification

Applicants have amended the Related Applications paragraph in the specification to update the status of the parent application, U.S. Application No. 09/454,204, thereby obviating the Examiner's objection.

Double Patenting

Claims 1-6, 10, 14-16, 27 and 31-33 are rejected on the ground of nonstatutory obviousness-type double patenting "as being unpatentable over claims 1, 2, 5-7, 15-18, and 20 of U.S. Patent No. 6,663,871" (Office Action, page 3).

Claims 1-3, 6, 7, 10, 12, 14 and 15 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting "as being unpatentable over claims 1, 4, 5, 9, 11, 13, and 14 of copending Application No. 10/833,439" and "over claims 1, 4, 5, 9, 11, and 13-16 of copending Application No. 10/833,744" (Office Action, page 4).

Claims 1-3, 5-7, 10, 12, 14 and 15 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting "as being unpatentable over claims 1, 4, 5, 9, 11, and 13-15 of copending Application No. 10/833,745" (Office Action, page 5).

Claims 1, 6 and 27 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting "as being unpatentable over claims 1-5 and 6-8 of copending Application No. 10/653,624" (Office Action, page 5).

According to the Examiner, although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are generic to the referenced claims of U.S. Patent No. 6,663,871 and U.S. Patent Application Nos. 10/833,439, 10/833,744, 10/833,745 and 10/653,624.

Once the present claims of the subject application are deemed allowable, Applicants will submit a terminal disclaimer if the allowable claims cover subject matter that is not patentably distinct from the subject matter covered by the claims of U.S. Patent No. 6,663,871 and/or if the allowable claims cover subject matter that is not patentably distinct from the subject matter covered by the claims of U.S. Patent Application Nos. 10/833,439, 10/833,744, 10/833,745

and/or 10/653,624. A terminal disclaimer is not an admission or comment regarding the merits of the rejection (Quad Environmental Technologies Corp. v. Union Sanitary District, 946 F.2d 870, 20 USPQ2d 1392 (Fed. Cir. 1991)).

Rejection of Claims 1, 2, 6, 7, 10, 12 and 14 under 35 U.S.C. §102(b)

Claims 1, 2, 6, 7, 10, 12 and 14 are rejected under 35 U.S.C. §102(b) "as being anticipated by Hodge *et al.* (1997, Apr-May, Ref. No. AU3 in IDS filed on 06 July 2004)" (Office Action, page 5). In the Examiner's opinion, Hodge *et al.* teach "a method of generating a CD8+ T cell immune response in mice against a tumor antigen by administering a replicating vaccinia virus vector for priming and a non-replicating avian pox virus vector, either the ALVAC derived from canarypox or fowlpox virus, for boosting the expression of an epitope, the human carcinoembryonic antigen (CEA)" (Office Action, page 6).

Applicants respectfully disagree. Hodge *et al.* teach that when mice were immunized with a recombinant vaccinia virus containing the human carcinoembryonic antigen (CEA) gene, designated rV-CEA, and then a canarypox (ALVAC) expressing the CEA antigen, designated ALVAC-CEA, "CEA-specific T-cell responses were at least four times greater, and far superior to those achieved with three immunizations of ALVAC-CEA" (Hodge *et al.*, abstract). In Table 2, Hodge *et al.* show enhancement of CEA specific lymphoproliferative responses of mouse T-cells after immunization with V-Wyeth and rV-CEA, followed by boosting with ALVAC-CEA. However, in the lymphoproliferative assay used by Hodge *et al.* to detect a T cell response, "purified human CEA", or whole CEA protein, was used as the antigen. The use of soluble CEA protein in the lymphoproliferative assay of Hodge *et al.* indicates that the responding T cells were ***CD4+ T cells***.

In support of this statement, a copy of a Declaration of Dr. Jörg Schneider, an inventor of the claimed subject matter, under 37 C.F.R. §1.132 (hereinafter "Declaration"), is being filed concurrently herewith as the Exhibit. The original Declaration was filed in the priority application, U.S. Application No. 09/454,204, now U.S. Patent No. 6,663,871, in support of the invention claimed therein. For the convenience of the Examiner, an unexecuted copy of the Declaration is also being submitted with this Amendment for clarity. As Dr. Schneider discusses in the Declaration, exogenous soluble protein, such as the CEA antigen, enter the MHC class II

presentation pathway, the pathway in which antigens are presented to CD4+ T cells. Exogenous soluble protein cannot readily enter the MHC class I presentation pathway, the pathway in which antigens are presented to CD8+ T cells.

Therefore, Hodge *et al.* clearly do not teach a method for generating a CD8+ T cell immune response in a mammal against at least one target antigen, comprising administering to the mammal a priming composition comprising a source of one or more CD8+ T cell epitopes of the target antigen and a boosting composition comprising a source of one or more CD8+ T cell epitopes of the target antigen, including at least one CD8+ T cell epitope which is the same as a CD8+ T cell epitope of the priming composition, wherein the source of CD8+ T cell epitopes is a non-replicating or replication-impaired recombinant virus vector in the mammal.

Rejection of Claims 1-4, 6, 7, 10, 12 and 14-16 under 35 U.S.C. §103(a)

Claims 1-4, 6, 7, 10, 12 and 14-16 are rejected under 35 U.S.C. §103(a) "as being unpatentable over Hodge *et al.* (1997) in view of Stoute *et al.* (1997)" (Office Action, page 6). The Examiner states that "[t]he instant invention is further limited to a SBAS2 adjuvant" and that "Hodge *et al.* does not disclose the SBAS2 adjuvant" (Office Action, page 6). The Examiner cites Stoute *et al.* as describing "malaria vaccine formulations in three kinds of adjuvants", including "an oil-in-water emulsion plus the immune stimulants monophosphoryl lipid A and QS21 (SBAS2)" (Office Action, page 7). According to the Examiner, Stoute *et al.* further describe that "SBAS2 is the most efficacious adjuvant" (Office Action, page 7). The Examiner asserts that:

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to formulate the priming and boosting compositions of Hodge *et al.* in the SBAS2 adjuvant as taught by Stoute *et al.* One having ordinary skill in the art would have been motivated to do this because SBAS2 may also provide signals required to up-regulate co-stimulatory molecules on antigen-presenting cells, induce expression of molecules that permit these cells to travel to target tissues, or induce production of cytokines that mediate protection, as per suggested by Stoute *et al.* There would have been a reasonable expectation of success, given the results that the SBAS2 formulation proved superior for inducing strong antibody responses and strong antigen-specific delayed hypersenstivity in primates and proliferative and cytolytic T cell responses in mice, as taught by Stoute *et al.*

(Office Action, page 7).

Applicants respectfully disagree. An obviousness rejection requires both (1) that "the prior art would have suggested to the person of ordinary skill in the art that they should . . . carry out the claimed process"; and (2) that the prior art should establish a reasonable expectation of success. In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in applicant's disclosure." Id. As discussed below, Hodge *et al.* teach away from methods using a non-replicating or replication-impaired recombinant virus vector in a heterologous prime-boost immunization.

Hodge *et al.*

Hodge *et al.* primed mice with a recombinant replication-competent vaccinia virus expressing human carcinoembryonic antigen (rV-CEA), followed by boosts with recombinant non-replicating avian pox virus containing CEA (ALVAC-CEA). Hodge *et al.* obtained the best antitumor responses using three homologous immunizations with rV-CEA or three homologous immunizations with ALVAC-CEA, compared to the heterologous prime/boost immunization as shown below:

•3 immunizations with rV-CEA	100% protection (page 767)
•3 immunizations with ALVAC-CEA	70% protection (page 764)
•1 rV-CEA prime followed by 2 ALVAC-CEA boosts	63% protection (5/8, page 766)
•1 rV-CEA prime followed by 1 ALVAC-CEA boost	50% protection (4/8, page 765)

Thus, the ***heterologous rV-CEA prime/ALVAC-CEA boost*** provided ***less protection*** than three ***homologous immunizations*** of either rV-CEA or ALVAC-CEA. Based on these findings, one of skill in the art would not have been motivated to carry out a heterologous prime-boost immunization protocol in an effort to induce an immune response (e.g., a CD8+ T cell response) in a mammal. Rather, the skilled artisan would have been motivated by the teachings of Hodge *et al.* to practice a homologous immunization method, preferably using the replication-competent rV-CEA.

Furthermore, Hodge *et al.* teach that "[i]t appears from these studies and other studies conducted in our laboratory that on a dose for dose basis, ALVAC-CEA may not be as potent in

inducing cellular immune responses as the recombinant vaccinia construct" (Hodge *et al.*, page 767, left column). This statement clearly teaches away from Applicants' claimed invention, which is based, in part, on Applicants' surprising discovery that non-replicating and replication-impaired viruses (e.g., ALVAC-CEA) elicit a significantly stronger boosting effect to a primed CD8+ T cell response than a corresponding replication-competent virus (e.g., rV-CEA), which would be expected to express higher levels of antigen than the non-replicating or replication-impaired counterpart. In fact, Hodge *et al.* disclose that "BSC-1 cells (10^7) infected with 10 MOI ALVAC-CEA for 12 h produced 1.48 ng of CEA per μg total protein. In contrast, cells infected with rV-CEA produced 6.06 ng of CEA per μg total protein" (Hodge *et al.*, page 762, left column). The teachings of Hodge *et al.* clearly direct one of skill in the art to use a replication-competent virus vector, rather than a non-replicating or replication-impaired virus vector, to elicit cellular immune responses (e.g., a CD8+ T cell response).

Stoute *et al.*

Stoute *et al.* immunized human subjects with "a hybrid in which the circumsporozoite protein fused to hepatitis B surface antigen (HBsAg) was expressed together with unfused HBsAg" (Stoute *et al.*, page 86, right column), and found that the vaccine "protects adults who have never been exposed to malaria against experimental challenge with *P. falciparum* sporozoites", and that "strong adjuvants were required, but comparison of the efficacy of SBAS2 (vaccine 3) with that of SBAS3 (vaccine 2) suggested that strong antibody responses to tandem-repeat epitopes alone were insufficient to confer protection" (Stoute *et al.*, page 90, left column). Stoute *et al.* further teach that "[e]ffective adjuvants such as those in SBAS2 may also provide signals required to up-regulate costimulatory molecules on antigen-presenting cells" (Stoute *et al.*, page 90, left column). Stoute *et al.* do not teach or suggest generating a CD8+ T cell immune response in a mammal against at least one target antigen, comprising administering to the mammal a priming composition comprising a source of one or more CD8+ T cell epitopes of the target antigen and a boosting composition comprising a source of one or more CD8+ T cell epitopes of the target antigen, including at least one CD8+ T cell epitope which is the same as the as a CD8+ T cell epitope of the priming composition, wherein the source of CD8+ T cells epitopes is a non-replicating or replication-impaired recombinant virus vector in the mammal.

Combination of Hodge *et al.* and Stoute *et al.*

One of skill in the art would not be motivated to combine the teachings of Hodge *et al.* and Stoute *et al.* in order to practice a heterologous immunization protocol using an rV-CEA priming composition and an ALVAC-CEA boosting composition, each formulated in SBAS2 adjuvant as taught by Stoute *et al.*, because Hodge *et al.* clearly teach away from Applicants' claimed invention for the reasons discussed above. Even if one were to make the improper combination, the combined teachings of the cited references clearly do not suggest to the person of ordinary skill in the art that they should generate a CD8+ T cell immune response in a mammal against at least one target antigen, comprising administering to the mammal a priming composition comprising a source of one or more CD8+ T cell epitopes of the target antigen and a boosting composition comprising a source of one or more CD8+ T cell epitopes of the target antigen, including at least one CD8+ T cell epitope which is the same as a CD8+ T cell epitope of the priming composition, wherein the source of CD8+ T cell epitopes in the boosting composition is a non-replicating or replication-impaired recombinant virus vector in the mammal.

Thus, the combined teachings of Hodge *et al.* and Stoute *et al.* do not render the claimed subject matter obvious.

Rejection of Claims 1-3, 6, 10, 12, 14 and 15 under 35 U.S.C. §103(a)

Claims 1-3, 6, 10, 12, 14 and 15 are rejected under 35 U.S.C. §103(a) "as being unpatentable over Pialoux *et al.* (1995) in view of Egan *et al.* (1995, IDS No. AU9 on 28 October 2004)" (Office Action, page 7). The Examiner cites Pialoux *et al.* as disclosing "a prime-boost approach to generate CD8+ T cell response against HIV, by injecting [healthy] adults with recombinant canarypox vector expressing the HIV-1 gp160" (Office Action, page 8). The Examiner cites Egan *et al.* as suggesting "administering non-replicating canarypox vectors expressing HIV gp160 from the MN isolate" (Office Action, page 8). The Examiner asserts that:

> It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify vectors of Pialoux *et al.* to non-replicating viral vectors. One having ordinary skill in the art would have been motivated to do this to ensure the safety of the immunogenic vectors in humans, as per suggested by

> Egan *et al.*, who established a reasonable expectation of success by describing the administration of non-replicating ALVAC vector for the induction of CD8+ HIV-1-specific CTL in adult humans.

(Office Action, page 8).

Applicants respectfully disagree. An obviousness rejection requires both (1) that "the prior art would have suggested to the person of ordinary skill in the art that they should . . . carry out the claimed process"; and (2) that the prior art should establish a reasonable expectation of success. In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in applicant's disclosure." Id.

Applicants' claimed invention is directed to a ***heterologous prime-boost*** vaccination method for generating a CD8+ T cell immune response in a mammal against at least one target antigen. The claimed method comprises administering to the mammal at least one dose of:

(i) a priming composition comprising a source of one or more CD8+ T cell epitopes of the target antigen; and

(ii) a boosting composition comprising a source of one or more CD8+ T cell epitopes of the target antigen, including at least one CD8+ T cell epitope which is the same as a CD8+ T cell epitope of the priming composition, wherein the source of CD8+ T cell epitopes in the boosting composition is a ***non-replicating or replication-impaired recombinant virus vector*** in the mammal.

In contrast to Applicants' claimed method, both Pialoux *et al.* and Egan *et al.* teach a heterologous prime-boost method that comprises administering to a human:

(i) a priming agent that is an ALVAC vector that expresses an HIV protein; and

(ii) a boosting agent that includes the recombinant HIV protein of (i).

Neither Pialoux *et al.* nor Egan *et al.* teach or suggest a ***heterologous*** prime-boost method in which the ***boosting agent/composition is a non-replicating or replication-impaired recombinant virus vector***.

Pialoux *et al.*

Pialoux *et al.* teach a heterologous prime-boost method for humans in which:

(i) ALVAC expressing HIV gp160 (ALVAC-HIV) was administered as the priming agent (i.e., vCP125); and

(ii) recombinant HIV gp160 was administered as the boosting agent.

Specifically, Pialoux *et al.* "evaluated the safety and the immunogenicity of a new combined vaccine regimen consisting of priming with a recombinant canarypox virus expressing gp160 (MN) [vCP125] followed by ***boosters with a soluble recombinant envelope glycoprotein gp160 (MN/LAI)*** [rgp160] in HIV-seronegative volunteers at low risk of HIV infection" (Pialoux *et al.*, page 374, left column; emphasis added). Pialoux *et al.* disclose that "[t]his prime-boost vaccine approach using a non-replicating recombinant live vector, ALVAC-HIV (vCP125), and an rgp160 was safe in humans and did induce both humoral and cell-mediated immune responses" (Pialoux *et al.*, Abstract). In addition, Pialoux *et al.* teach that "[t]he results presented here ***make it compelling*** to pursue the approach of ***priming with recombinant live avipox vectors*** such as canarypox followed by ***envelope and/or core subunit boosting*** in order to elicit both functional humoral and cellular immune responses" (Pialoux *et al.*, page 380, right column; emphasis added). Pialoux *et al.* do not disclose or suggest a ***heterologous*** prime-boost method for generating a CD8+ T cell immune response against a target antigen in a mammal that comprises administering a ***boosting composition comprising a non-replicating or replication-impaired recombinant virus vector.***

Notably, the heterologous prime-boost method disclosed by Pialoux *et al.* was intended "to elicit ***both functional humoral and cellular immune responses***" (Pialoux *et al.*, page 380; emphasis added) against HIV in humans by administering a combination of an ALVAC-HIV, which is known to induce CD8+ T cell responses against HIV, and recombinant gp160 protein, which is known to induce antibody responses against HIV (see, e.g., Pialoux *et al.*, page 374, right column and page 379). Specifically, Pialoux *et al.* teach that "[r]ecombinant proteins can usually prime $CD4^+$ cells to induce ***antibody responses***, but they are ***generally ineffective at inducing $CD8^+$ CTLs***" and that "[i]n contrast, recombinant vaccinia viruses infect target cells, resulting in intracellular expression of viral genes, and ***effectively induce class I-restricted CD8+ CTL responses***" (Pialoux *et al.*, page 379; emphasis added). Pialoux *et al.* further disclose that "[t]wo injections of ALVAC-HIV (vCP125) did not elicit antibodies. Combining vCP125 with one boost of rgp160 resulted in antibody and T cell responses" (Pialoux *et al.*, page 380).

Thus, Pialoux *et al.* employed a combination of ALVAC-HIV and recombinant gp160 protein immunizations to induce T cell and antibody immune responses against HIV, respectively. Pialoux *et al.* do not teach or suggest that a recombinant gp160 protein should be used in a heterologous prime-boost method to boost a CD8+ T cell response against HIV in a human. Rather, Pialoux *et al.* suggest that immunization with ALVAC-HIV alone is sufficient to induce a CD8+ T cell response against HIV in a human.

In contrast to the heterologous prime-boost method described by Pialoux *et al.*, Applicants claimed method is a method of generating a CD8+ T cell immune response in a mammal against at least one target antigen involving the use of a non-replicating or replication-impaired recombinant virus vector to ***boost a primed CD8+ T cell response***.

Egan *et al.*

Egan *et al.* teach a heterologous prime-boost method in which:

(i) ALVAC expressing the HIV glycoprotein (i.e., vCP125); and

(ii) recombinant HIV gp120,

were administered to humans as priming and boosting agents, respectively, and compare this method to an immunization regimen in which multiple doses of vCP125 were administered to humans. Like Pialoux *et al.*, Egan *et al.* teach that "an effective vaccine against human immunodeficiencey virus type I (HIV-1) may require immunization regimens that elicit both cytolytic T lymphocyte (CTL) and neutralizing antibody responses" (Egan *et al.*, page 1623, left column).

Egan *et al.* disclose that the "purpose of this study was to determine whether HIV-1-specific CTL responses could be induced in seronegative human volunteers by ***a vaccine regimen involving initial priming with a live recombinant canarypox virus*** expressing the HIV-1_{MN} *env* gene" (Egan *et al.*, page 1623, right column; emphasis added). In particular, Egan *et al.* tested "whether immunization with ***ALVAC alone or in combination with subunit boosting*** could induce CTL in vaccinia-immune and -naive volunteers" (Egan *et al.*, abstract; emphasis added). Specifically, Egan *et al.* disclose that "[t]welve volunteers were primed . . . with 10^6 $TCID_{50}$ ALVAC-HIV and immunized . . . with either ALVAC-HIV (7 volunteers) or purified recombinant HIV-1 gp120 in MF59 (5 volunteers)" (Egan *et al.*, page 1624, left column). Egan *et*

al. conclude that the "results indicate that low doses of a nonreplicating virus vector ***alone*** can elicit both $CD4^+$ and $CD8^+$ HIV-1-specific CTL in a subset of seronegative volunteers" (Egan *et al.*, abstract, emphasis added). Thus, Egan *et al.* do not teach or suggest that their prime-boost protocol featuring immunization with ALVAC-HIV as a priming vector is preferable or superior to immunization with ALVAC-HIV alone.

Combination of Pialoux *et al.* and Egan *et al.*

The combination of Pialoux *et al.* and Egan *et al.* teach a heterologous prime-boost method that involves ***priming with vCP125, an ALVAC expressing an HIV glycoprotein,*** and ***boosting with a recombinant HIV protein*** (i.e., HIV gp160 or HIV gp120). Neither Pialoux *et al.* nor Egan *et al.* teach or suggest a ***heterologous*** prime-boost method for generating a CD8+ T cell immune response in a mammal against at least one target antigen that comprises administering a ***boosting composition comprising a non-replicating or replication-impaired recombinant virus vector.***

Pialoux *et al.* teach a vaccination technique intended to produce both cellular and antibody immune responses. Pialoux *et al.* observed that ALVAC produces some level of cellular immune response but little antibody response. A recombinant protein boost was then used to induce an ***antibody response***. Egan et al teach that "[p]rotocols were designed to determine whether immunization with ALVAC alone or in combination with subunit boosting could induce CTL in vaccinia-immune and -naive volunteers" (Egan *et al.*, abstract") and that subunit boosting did not increase the cellular immune response compared to immunization with ALVAC alone. Based on the teachings in Pialoux *et al.* that their results "make it compelling to pursue the approach of priming with recombinant live avipox vectors such as canarypox" (Pialoux *et al.*, page 380, right column) and in Egan *et al.* that "[i]n each of the volunteers with a positive CTL response, the response could be attributed to immunization with ALVAC-HIV" (Egan *et al.*, page 1627, left column) and that "low doses of a nonreplicating virus vector alone can elicit both $CD4^+$ and $CD8^+$ HIV-1-specific CTL in a subset of seronegative volunteers" (Egan *et al.* abstract), one of skill in the art would have been motivated to carry out a ***homologous*** prime-boost method in humans using multiple doses of vCP125 to generate a CD8+ T cell immune response against HIV in a

human. Clearly, the cited references, either alone or in combination, would not have motivated one of skill in the art to practice Applicants' claimed method.

Thus, the combined teachings of Pialoux *et al.* and Egan *et al.* do not render Applicants' claimed invention obvious.

Rejection of Claims 1-3, 5, 6, 10, 12, 14 and 15 under 35 U.S.C. §103(a)

Claims 1-3, 5, 6, 10, 12, 14 and 15 are rejected under 35 U.S.C. §103(a) "as being unpatentable over Pialoux *et al.* (1995) in view of Egan *et al.* (1995), and further in view of Walker *et al.* (1989)" (Office Action, page 9). According to the Examiner, "Walker *et al.* explicitly suggests HIV-1 epitope in the reverse transcriptase of the amino acid sequence, NPDIVIYQYMDDLYVGSDLEIGQHR (peptide 50) to specifically stimulate CD8+ T cell immune response" (Office Action, page 9). The Examiner asserts that:

> It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the epitope of Pialoux *et al.* and Egan *et al.* to the epitope comprising an amino acid sequence of SEQ ID NO:64. One having ordinary skill in the art would have been motivated to do this because the peptide 50 has been clearly defined as a potent CTL epitope from the most highly conserved region of [the] HIV genome, as per suggested by Walker *et al.*, who established a reasonable expectation of success by describing that this epitope induces specific cytotoxicity in target cells.

(Office Action, page 9).

Applicants respectfully disagree. As discussed above, the combined teachings of Pialoux *et al.* and Egan *et al.* do not render Applicants' claimed invention obvious. Walker *et al.* clearly do not provide the teaching that is lacking in the Pialoux *et al.* and Egan *et al.* references that would render Applicants' claimed invention obvious for the reasons discussed below.

Walker *et al.* disclose the generation of "seven HIV-1 reverse transcriptase-specific cytotoxic T-lymphocyte (CTL) clones from the peripheral blood of two seropositive subjects" (Walker *et al.*, abstract). Walker *et al.* teach that three of these seven lines were able to lyse cells incubated with peptide 50, which consists of the amino acid sequence NPDIVIYQYMDDLYVGSDLEIGQHR, in a CTL lysis assay *in vitro* (Walker *et al.*, page 9517, Table 4). Walker *et al.* do not teach or suggest that the disclosed CTL epitopes should be featured in a prime-boost method for generating a CD8+ T cell immune response in a mammal against a

target antigen (e.g., HIV), nor do Walker *et al.* disclose or suggest administering to a mammal a boosting composition comprising a non-replicating or replication-impaired recombinant virus vector that is a source of any of the disclosed CD8+ T cell epitopes.

As stated above, the combination of Pialoux *et al.* and Egan *et al.* teach a heterologous prime-boost method that involves ***priming with vCP125***, an ALVAC expressing an HIV protein, and ***boosting with a recombinant HIV protein*** (i.e., HIV gp160 or HIV gp120). Neither Pialoux *et al.* nor Egan *et al.* teach or suggest a ***heterologous*** prime-boost method for generating a CD8+ T cell immune response in a mammal against a target antigen that comprises administering a ***boosting*** composition comprising a non-replicating or replication-impaired recombinant virus vector. Walker *et al.* also do not teach or suggest a ***heterologous*** prime-boost method for generating a CD8+ T cell immune response in a mammal against a target antigen that comprises administering a ***boosting*** composition comprising a non-replicating or replication-impaired recombinant virus vector.

Based on the teachings in Pialoux *et al.* that their results "make it compelling to pursue the approach of priming with recombinant live avipox vectors such as canarypox" (Pialoux *et al.*, page 380, right column) and in Egan *et al.* that "[i]n each of the volunteers with a positive CTL response, the response could be attributed to immunization with ALVAC-HIV" (Egan *et al.*, page 627, left column) and that "low doses of a nonreplicating virus vector alone can elicit both $CD4^+$ and $CD8^+$ HIV-1-specific CTL in a subset of seronegative volunteers" (Egan *et al.* abstract), the combined teachings of Pialoux *et al.*, Egan *et al.*, and Walker *et al.*, would have directed one of skill in the art to carry out a ***homologous*** prime-boost method in humans using an ALVAC vector that expresses peptide 50. The combined teachings of these references clearly would not have motivated one of skill in the art to carry out Applicants' claimed method.

Thus, the combined teachings of Pialoux *et al.*, Egan *et al.* and Walker *et al.* do not render Applicants' claimed invention obvious.

Supplemental Information Disclosure Statement

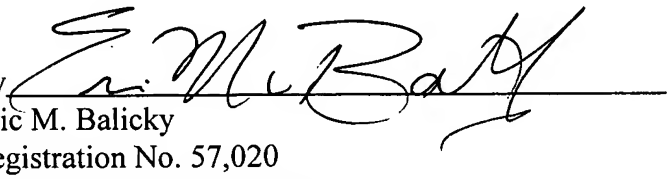
A Supplemental Information Disclosure Statement (SIDS) is being filed concurrently herewith. Entry of the SIDS is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By 

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